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EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,579	GULATI, ANIL	
	Examiner	Art Unit	
	KENDRA D. CARTER	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,13,15 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,13,15 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of February 19, 2009 made to the office action filed August 20, 2008. Claims 1, 9, 13, 15 and 19-24 are pending. No claims were amended.

The Applicant's arguments of the following 35 U.S.C. 103(a) rejection were found not persuasive and thus are maintained: 1) claims 1 and 9 as being unpatentable over Hughes et al. in view of Wu; and 2) claims 13, 15 and 19-24 as being unpatentable over Hughes et al. in view of Wu as applied to claims 1 and 9 above and in further view of Woolf.

The above rejections have been modified to address the Applicant's arguments. The Examiner addressed the Applicants arguments after the rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(1) Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al. (US 2003/0040534 A1) in view of Wu (Expert Opinion on Therapeutic Patents, 2000, Vol. 10, No. 11, pp. 1653-1668).

Hughes et al. teaches a compound that is an endothelin antagonist of ET-1 and ET-2, and are useful in treatment of conditions associated with increased ET levels and of all endothelin-dependent disorders such as for the treatment of Alzheimer's dementia (see page 2, paragraph 11, lines 1-5 and paragraph 18 in its entirety).

Hughes et al. does not teach the Applicant's elected endothelin antagonist compound bosentan.

Wu teaches that endothelins (ETs) exert their biological effects such as physiological and pathological conditions by binding to the ET_A (binds ET-1 more than ET-2 or ET-3) and ET_B (binds ET-1, ET-2 and ET-3 equally) (see page 1653, introduction in its entirety). The drug bosentan is an endothelin antagonist, particularly a mixed ET_A/ET_B antagonist that has even been used in clinical trials (see page 1658, section 2.3, in particular.) Mixed ET_A/ET_B antagonist are used to lower blood pressure, protect against ischaemia-induced neuronal degeneration (see page 1658-1661, ET_A/ET_B balanced antagonists). ET_A or mixed ET_A/ET_B antagonist may be useful in the

treatment of conditions such as prostate cancer, male erectile dysfunction and vascular remodeling. The debate continues over whether ET_A or mixed ET_A/ET_B antagonist are more therapeutically useful, but studies have shown that selective ET_B antagonist compounds are not beneficial (see page 1665, column 1, lines 3-6 and 14-17).

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious and motivated to provide the bosentan of Wu in the treatment of Alzheimer's dementia as taught by Hughes et al, because Hughes et al. teaches that Alzheimer's dementia is associated with increased ET levels and can be treated by providing endothelin antagonists having ET1/ET2 antagonist activity (which is directly associated with ET_A and ET_B), whereas Wu teaches that bosentan is a compound having known ET_A/ET_B mixed antagonist activity. In other words, since the ETs must bind to the ET_A and ET_B receptors to exert their biological effects (such as Alzheimer's dementia), an antagonist of ET_A and ET_B inhibits the ability of the excess ET levels to exert their biological effect. Thus, one of ordinary skill in the art would have been motivated to provide the bosentan in the method of Hughes et al. with the expectation of providing a compound capable of treating Alzheimer's disease. Accordingly, claim 1 is obvious over the teachings of Hughes et al. and Wu.

In regards to the limitation of a administering to a human suffering from Alzheimer's disease, the Examiner reads the treatment of Alzheimer's dementia to meet

this limitation. One who has Alzheimer's dementia has Alzheimer's disease and Hughes et al. treats this ailment, and thus treats Alzheimer's disease.

(2) Claims 13, 15 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al. (US 2003/0040534 A1) in view of Wu (Expert Opinion on Therapeutic Patents, 2000, Vol. 10, No. 11, pp. 1653-1668) as applied to claims 1 and 9 above in further view of Woolf (US 5,466,696).

The teachings of Hughes et al. and Wu are as applied to claims 1 and 9 above.

Hughes et al. and Wu do not teach a cholinesterase inhibitor, particularly the Applicant's elected compound tacrine as disclosed in claims 13 and 15. Hughes et al. and Wu also do not teach treatment regime disclosed in claims 19-24.

Woolf teaches tacrine and cytochrome P450 oxidase inhibitors and methods of use (see title). Clinical studies have been performed on patient's suffering from Alzheimer's disease by utilizing tacrine (see column 1, lines 26-27).

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious and motivated to provide the tacrine of Woolf in the endothelin antagonist Alzheimer's dementia treatment method of Hughes et al. in view of Wu, because Hughes et al. teach a method of treating Alzheimer's

dementia. Thus, both Hughes et al. and Woolf teach treatments of Alzheimer's disease. Therefore, it is considered that one of ordinary skill in the art would have been motivated to provide tacrine in the Alzheimer's treatment method of Hughes et al. in view of Wu, with the expectation of providing a compound capable of treatment of the condition. Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.) Accordingly, claims 13 and 15 are considered to be obvious over the teachings of Hughes et al. in view of Wu in further view of Woolf

Regarding claims 19-24, Hughes et al. in view of Wu in further view of Woolf render obvious providing a combination therapy of the endothelin antagonist bosentan and the ACE inhibitor tacrine for the treatment of Alzheimer's disease. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the treatment regime, such as by providing the therapeutic agents in the same or separate compositions, or by administering one of the compounds prior to the other, according to the guidance provided by Hughes et al. in view of Wu in further view of Woolf, to provide the desired Alzheimer's treatment. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges

by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.) It is furthermore noted that, regarding the order of administration as recited in claims 23-24, it has been held that merely changing the order of steps in a multi-step process is not a patentable modification absent a showing of unexpected results. *Ex parte Rubin* 128 USPQ 440 (POBA 1959.)

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

> The Applicant argues that no conclusion can be made as to which type of endothelin antagonist the compound of the '534 publication belongs. The Wu publication, in Table 1, shows that no single endothelin antagonist (ET_A or ET_A/ET_B) is contemplated as being useful for all disease states. Accordingly, the Wu publication table shows that an ET_A antagonist and an ET_A/ET_B antagonist is useful in the treatment of others. Therefore, the efficacy of an ET_A antagonist cannot be equated to the efficacy of an ET_A/ET_B antagonist in the treatment of the same disease. Thus, the Examiner has shown hindsight reconstruction.

The Examiner respectfully disagrees, and notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Although Hughes et al. does not teach which type of endothelin antagonist the compound is, it is recognized that endothelin antagoinist treat Alzheimer's dementia because the disease

results in the increase of ET levels (see page 2, paragraph 11, lines 1-5 and paragraph 18 in its entirety). The Wu reference provides further teaching of enothelin antagonists in general and particularly the applicant's elected compound. Thus, if endothelin antagonist treat Alzheimer's dementia, and bosentan is a compound having known ET_A/ET_B mixed antagonist activity, one of ordinary skill in the art would have been motivated to provide the bosentan in the method of Hughes et al. with the expectation of providing a compound capable of treating Alzheimer's disease. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

> The Applicant argues that ET_A and ET_B receptors act opposite to one another and give different responses. Hughes et al. ('534 publication) enables no more than ET_A receptor antagonism and does not disclose which ET the compound antagonizes. Additionally, Hughes et al. does not provide guidance if the compounds inhibit or activate ET_A. The Wu reference does not teach or suggest the use of an endothelin antagonist in the treatment of Alzheimer's Disease, and the fact that bosentan is in clinical trials is irrelevant with respect to the claims at issue. The examiner makes contradictory statements in that selective ET_B antagonist compounds are not beneficial, then stating that positive responses are known from antagonizing both ET_A and ET_B receptors. Additionally the examiner states that one skilled in the art would try the compound of Wu

> in *hopes* that the mixed antagonist would be effective to treat Alzheimer's dementia. On the contrary, individual endothelin antagonist are used to treat different diseases, with very little overlap. Therefore, the examiner can not rely upon an obvious to try" rationale.

The Examiner disagrees because although the ET_A and ET_B receptors can have different responses, it is also known that mixed ET_A/ET_B antagonist are used to lower blood pressure, protect against ischaemia-induced neuronal degeneration (see Wu, page 1658-1661, ET_A/ET_B balanced antagonists). Thus, Wu provides teachings that the two receptors do not work against each other and that positive responses can occur from antagonizing both receptors.

In regards to bosentan being in clinical trials, Wu provides a teaching that bosentan is a drug that is considered to be an endothelin antagonist enough to be put in clinical trials.

In regards to the contradictory statements, the Examiner would like to clarify that selective ET_B antagonist were found not to be beneficial, but ET_A and mixed ET_A/ET_B antagonist are therapeutic (see page 1665, column 1, lines 3-6 and 14-17).

The Examiner would further like to note that Hughes provides the teaching that entothelin antagonist of ET-1 and ET-2 are useful in treating endothelin-dependent disorders such as Alzheimer's dementia (see page 2, paragraph 11, lines 1-5 and paragraph 18 in its entirety). Again, it is important to note that both ET_A and ET_B bind to ET-1 and ET-2, but at different specificities as taught by Wu. Thus, upon antagonizing ET_A or mixed ET_A/ET_B one antagonizes ET-1 and ET-2.

In regards to the obvious to try rationale, Hughes et al. provides the teaching of the mechanism of action that treats Alzheimer's dementia (providing predictability and expectation of success), and Wu provides teaching that the applicant's compound works in the same mechanism of action. Therefore, one skilled in the art would find it obvious to try a drug that works on the mechanism of action that treats Alzheimer's dementia.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. D. C./
Examiner, Art Unit 1617

/SREENI PADMANABHAN/
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